REMARKS

I. The Invention

The present invention describes a recombinant vector useful for inducing a tumor-specific immune response against B-cell lymphoma, by way of a fusion protein of a cytokine and a tumor-specific idiotype. Rather than directly encoding the fusion protein, which would require individual cloning of the idiotype of every patient's lymphoma cells, the expression vector of this invention includes a sequence of at least 1.5 kb that is homologous to a region of the μ intron or the k intron, such that, following transfection of a B lymphoma cell and subsequent homologous recombination, the DNA sequences coding a cytokine and a immunoglobulin constant region (or a part thereof) also present in the vector are incorporated into the malignant B cell's genomic sequence. A cytokine fusion protein is then produced by the B cell to include the specific idiotype encoded by the endogenous sequence of the malignant B cell. After rendered incapable of proliferation, such a malignant B cell expressing a tumor immunoglobulin-cytokine fusion protein can be reintroduced into a patient to elicit a specific anti-B cell lymphoma immunity due to enhanced recruitment of antigen-presenting cells by the cytokine and more effective presentation of the tumor-specific immunoglobulin idiotype. This invention eliminates the need to clone each patient's idiotypic domain and is thus quick, convenient, and less expensive.

II. Status of the Claims

Claims 1-17 were under examination. Claims 18-24 have been canceled, and claims 25-30 have been withdrawn from consideration. Upon entry of the present amendment, claims 6, 10, 25-28, and 30 are canceled. An article is added to each of the remaining claims. Claim 1 is amended to recite "a constant region of an immunoglobulin" and "a part of the constant region," which finds support in, *e.g.*, original claim 6. Claims 11-14 are amended to harmonize with language of claim 1. Claim 15 is amended to replace plural form with singular form. Also, claim 1 is amended to correct a typographic error, and claim 12 is amended to improve clarity. No new matter is introduced.

III. Restriction Requirement

The Restriction Requirement mailed October 10, 2006, divided claims 1-17 and 25-30 into two Groups: Group I, claims 1-17, drawn to a vector; and Group II, claims 25-30, drawn to use of the vector. Applicant has elected the claims of Group I for prosecution. A closer review of the claims reveals, however, that claim 29, drawn to a malignant B cell comprising the vector of claim 1, has been erroneously included in Group II while it clearly belongs to Group I. As such, Applicant respectfully requests the Examiner to consider rejoining claim 29 with the elected claims for examination.

III. Information Disclosure Statement

The Examiner indicated that German Patent Application DE 4406512C1, cited as Reference B in the IDS filed on November 18, 2003, has not been considered since no English version was provided. Applicants are still in the process of obtaining the English version of this reference, which will be provided in a supplemental IDS as soon as available.

IV. Claim Objections

Claims 1-17 are objected to for lacking articles. Since amendment has been made to these claims as requested by the Examiner, this objection is fully addressed.

V. Claim Rejections

A. 35 U.S.C. §112, First Paragraph: Enablement

Claims 1-17 are rejected under 35 U.S.C. §112, first paragraph, for alleged lack of enablement. Applicant respectfully traverses the rejection.

A claimed invention is enabled when the disclosure allows one of ordinary skill in the art to make and use the invention without undue experimentation. MPEP §2164.01. The test for enablement is set forth in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). The consideration of multiple factors is necessary: the breadth of the claims; the nature of the invention; the state of the prior art; the level of predictability in the art; the amount of direction provided by the inventor; the existence of working examples; and the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In the present case, the claims are directed to a vector for expressing immunoglobulin-cytokine fusion proteins in malignant B cells. The vector comprises the following components operably linked to each other: (a) a region of at least 1.5 kb that is homologous to a region of the μ intron or the *k* intron; (b) at least one DNA sequence encoding a constant region of an immunoglobulin or a part of the constant region; (c) a DNA sequence encoding a cytokine; and (d) a marker gene that is selectable in eukaryotic B cells and contains a functional enhancer region. At the time this application was filed, the art of immunology and molecular biology was already highly advanced. The knowledge of immunoglobulin and cytokine genes was abundant and detailed, and the techniques in molecular cloning and recombinant gene expression were well developed and routinely employed. Therefore, a skilled artisan would know (a) what the μ intron or *k* intron sequence is and how to obtain a homologous sequence to the intron sequence that would permit homologous recombination; (b) how to obtain a coding sequence for an immunoglobulin constant region or a portion thereof; (c) how to obtain a cytokine coding sequence; and (d) how to obtain a selection marker useful in eukaryotic B cells and a functional enhancer region. Finally, a skilled artisan would also know how to arrange the sequences of (a)-(d) to make an expression vector for the intended process of transfection, recombinantion, expression, and selection. Because an artisan would know how to perform each and every step necessary to practice the claimed invention, the invention is fully enabled.

In making the enablement rejection, the Examiner argues that (1) the state of the art is advanced and the skill level is high (see, *e.g.*, page 5 of the Office Action of March 5, 2007); (2) cytokine-immunoglobulin fusions are known in the art for enhancing immune response, and construction of expression vectors for such fusions is "old" and "common place" (see, *e.g.*, pages 5 and 6 of the Office Action); and (3) the claims are excessively broad because they cover a genera of vectors comprising a genera of cytokines, enhancers, selection markers, and μ or *k* intron homologous sequences, *etc.*, whereas no guidance is given for one to select the type of cytokine, enhancer, μ or *k* intron homologous sequence to use in constructing the vector (see, *e.g.*, pages 6 and 8 of the Office Action). The Examiner also argues that a skilled artisan

would not know how to select or create a non-functional enhancer (see, *e.g.*, page 7 of the Office Action).

As an initial matter, the expression vector of this application is not a conventional expression vector that directly encodes fusion protein of a cytokine and a tumor-specific antibody. As already discussed in the first section of REMARKS, the expression vector utilizes the mechanism of homologous recombination naturally occurring within a B lymphoma cell to achieve the expression of a cytokine fusion protein that is tumor-specific (therefore induces a tumor-specific immunity) yet originated from a universal vector.

Applicant is in complete agreement with the Examiner regarding the vast amount of knowledge and high level of technical sophistication in the art. Applicant cannot agree, however, that enablement is lacking because the present disclosure does not provide guidance for one to select a specific cytokine, enhancer, μ or k intron homologous sequence, *etc.* What the law requires under 35 U.S.C. §112, first paragraph, is that a patent application describes the claimed invention in a manner that allows one of ordinary skill in the art to practice the invention without undue experimentation. As the Examiner has correctly recognized, the use of various cytokines as fusion partners for inducing a desired immune response was known in the art, see, *e.g.*, pages 5 and 6 of the Office Action (naming GM-CSF, IL-2, IL-4 as examples). Thus, a skilled artisan would know, upon reading the present disclosure, that he can choose from a list of known cytokines to construct his expression vector and he is fully capable of doing so, given the available tools in molecular cloning. Similarly, many different enhancers, selection markers, regulatory sequences, *etc.*, would also be known and available to the artisan for his choosing in making his expression vector. It would be well within the artisan's purview to select specific components for constructing an expression vector of this invention. Whether or not the specification teaches the selection of any particular cytokine, enhancer, regulatory sequence, selection marker, *etc.*, therefore has no bearing on the question of enablement.

In addition, the skilled artisan would also known various alternative means to render an enhancer non-functional, such as mutations, deletions, or substitutions (which the Examiner has recognized on page 7 of the Office Action). Although some testing may be needed

to confirm a newly manipulated enhancer as non-functional, such testing is nothing more than routine experimentation for the art. It is settled law that the enablement requirement does not preclude all experimentation, so long as the necessary experimentation is the type routinely conducted in the art. This is precisely the case here.

In summary, Applicant believes that the disclosure by the present application is sufficiently enabling for a person with ordinary skill in the art to practice the claimed invention and that no undue experimentation is required. The rejection for inadequate enablement should thus be properly withdrawn.

B. 35 U.S.C. §112, First Paragraph: Written Description

Claims 1-17 are rejected under 35 U.S.C. §112, first paragraph, for alleged inadequate written description. Applicant respectfully traverses the rejection.

According to the MPEP, to satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail such that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention at the time of filing. Possession of a claimed invention may be demonstrated by description of the invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. MPEP §2163 I.

The pending claims are drawn to a vector for expressing immunoglobulin-cytokine fusion proteins in malignant B cells. The vector comprises the following components operably linked to each other: (a) a region of at least 1.5 kb that is homologous to a region of the μ intron or the k intron; (b) at least one DNA sequence encoding a constant region of an immunoglobulin or a part of the constant region; (c) a DNA sequence encoding a cytokine; and (d) a marker gene that is selectable in eukaryotic B cells and contains a functional enhancer region. Thus, the common components of the claimed vector are provided. Because much was already known in immunology, and basic technologies in molecular biology were mature and frequently practiced when this application was filed, a skilled artisan would have sufficient knowledge of the common components of the claimed vector and how to acquire them. As

discussed in the last section, the artisan would have knowledge of a μ intron or k intron sequence and how to prepare a sequence that is homologous to the intron sequence and would permit homologous recombination at the intron site. The artisan would have knowledge of a coding sequence for an immunoglobulin constant region or a portion thereof. The artisan would also have knowledge of cytokine gene sequences. The artisan would in addition have knowledge of selection markers and functional enhancer regions. Recognizing that all required components of the vector can be readily made and that the assembled vector can be readily tested for its intended function, an ordinarily skilled artisan therefore would, upon reading the instant application, reasonably conclude that the inventor had in his possession the claimed invention at the time this application was filed.

When making the written description rejection, the Examiner argues that the description in the specification is insufficient because the claims encompass a genera of vectors comprising a genera of cytokines, enhancers, selection markers, and μ or k intron homologous sequences, *etc.*, but their distinguishing characteristics are not described. The Examiner also contends that written description is inadequate because only one species is described in the specification, whereas numerous other species are not described (see page 11 of the Office Action).

Applicant respectfully disagrees. First of all, the distinguishing characteristics of the claimed vectors are indeed described--by way of reciting common components of the vector, such as a μ or k intron homologous region, a DNA coding sequence for an immunoglobulin constant region or a part thereof, a DNA coding sequence for a cytokine, a marker gene selectable in eukaryotic B cells, and a functional enhancer region. Not only are the characteristics of each component provided throughout the specification, such characteristics are also well known to those of skill in the art at the time of filing of this application.

Second, as far as the number of representative species is concerned, the MPEP clearly states that "[w]hat constitutes a 'representative number' is an inverse function of the skill and knowledge in the art" and that there are situations "where one species adequately supports a genus." MPEP §2163 II.A.3 (a) ii). In view of the exceptionally high skill level and broad range

of knowledge in the pertinent field, Applicant believes that the instant case is indeed a situation where a single species sufficiently supports a genus.

In summary, considering the state of the art and the disclosure of this application, Applicant contends that features commonly shared by the claimed vectors have been described in detail, which "clearly allow persons of ordinary skill in the art to recognize that [the applicant] invented what is claimed." *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991). As such, Applicant respectfully requests that the Examiner withdraw the written description rejection.

C. 35 U.S.C. §112, Second Paragraph

Claims 1-17 are also rejected under 35 U.S.C. §112, second paragraph, for alleged indefiniteness. Specifically, the Examiner contends that, without an upper limit of the size of the sequence "at least 1.5 kb which is homologous to a region of the μ intron or the *k* intron," the metes and bounds of the claims are not limited. Applicant respectfully yet strongly disagrees. The requirement under 35 U.S.C. §112, second paragraph, is intended to ensure that a claimed invention is defined with reasonable clarity so as to inform the public of the boundaries of what constitutes infringement of a patent. MPEP §2173. The language "at least 1.5 kb" does not fail to define the metes and bounds of the claimed subject matter, because a skilled artisan (or even a lay person) would be able to understand what this language defines: a DNA sequence in the length of 1.5 kb or longer. For a given DNA sequence of any size, the public will be able to ascertain whether such DNA sequence is or is not "at least 1.5 kb." The Examiner has provided no explanation as to why there would be any difficulty for the public to do so.

Furthermore, if the Examiner's reasoning were correct that indefiniteness arises whenever an upper limit is omitted, then no U.S. patents should have ever been issued with the claim language of "at least." Yet a quick search at the USPTO web site indicates a total of 1503 patents containing "at least" in the claims. In 2007 alone, 106 such patents have issued. The rejection for the use of "at least" is unfounded and should be properly withdrawn.

The Examiner also objected to the term "derived from" in claim 12, which recites in the pertinent part, "domains derived from mouse, rat, goat, horse, or sheep," for allegedly being unclear and confusing. Since claim 12 has been amended and no longer recites the word "derived from," this particular rejection is overcome.

Withdrawal of the rejections under 35 U.S.C. §112, second paragraph, is therefore respectfully requested.

D. 35 U.S.C. §102

Claims 1-9, 11, and 15-17 are also rejected under 35 U.S.C. §102(e) for alleged anticipation by Polack (U.S. Patent No. 6,521,449). Applicant respectfully traverses the rejection.

To anticipate a pending claim, a prior art reference must provide, either expressly or inherently, each and every limitation of the pending claim. MPEP§2131. The pending claims of this application are directed to a vector for expressing an immunoglobulin-cytokine fusion protein in malignant B cells. The vector comprises the following components operably linked to each other: (a) a region of at least 1.5 kb which is homologous to a region of the μ intron or the k intron; (b) at least one DNA sequence encoding a constant region of an immunoglobulin or a part of the constant region; (c) a DNA sequence encoding a cytokine; and (d) a marker gene that is selectable in eukaryotic B cells and contains a functional enhancer region. At least one limitation of the pending claims, *e.g.*, the region of at least 1.5 kb which is homologous to a region of the μ intron or the k intron recited in (a) cannot found in the Polack reference after a careful review of the document. The Examiner points to column 8, line 4, for description of a coding sequence of 2.6 kb (see page 13, in the paragraph bridging pages 13 and 14, of the Office Action mailed March 5, 2007), presumably as an attempt to identify this claim limitation in Polack. This passage, however, relates to a coding sequence for Epstein Bar Virus (EBV) nuclear antigen 1 in the EBV genome. In contrast, the sequence of (a) is a homologous sequence to a region of a μ or k intron, not a coding sequence for an EBV protein.

As such, the Polack reference fails to provide every limitation of the pending claims and cannot anticipate the claims. Withdrawal of the rejection under 35 U.S.C. §102(e) is respectfully requested.

E. 35 U.S.C. §103

Claims 1-13 and 15-17 are further rejected under 35 U.S.C. §103(a) for alleged obviousness over Polack in view of Levy (U.S. Patent No. 6,009,846) and Gillies (U.S. Patent No. 5,650,150). Applicant respectfully traverses the rejection.

In order to establish a *prima facie* showing of obviousness, three requirements must be satisfied: all limitations of a pending claim must be expressly or impliedly disclosed by prior art references; there must be a suggestion or motivation in the art for one skilled artisan to combine the limitations; and there must be a reasonable expectation of success in making such a combination. MPEP §2143. As discussed in the last section, the primary reference by Polack *et al.* fails to provide all limitations of the pending claims. On the other hand, the secondary references, Levy and Gillies, are cited to provide teaching of a vector encoding an idiotype/GM-CSF fusion protein and a vector encoding a recombinant antibody-cytokine fusion protein, respectively (see page 16 of the Office Action). These two references also fail to provide at least this missing element, namely the region of at least 1.5 kb which is homologous to a region of the μ intron or the k intron recited in (a) of claim 1.

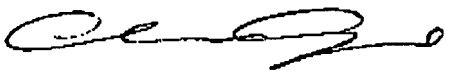
Without providing all claim limitations, the three cited references cannot support a *prima facie* case of obviousness. Accordingly, the rejection under 35 U.S.C. §103(a) cannot be sustained.

CONCLUSION

In view of the foregoing, Applicant believes that all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



Chuan Gao
Reg. No. 54,111

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 415-576-0200
Fax: 415-576-0300
CG:cg
61099142 v1